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EXAMINER	
EPPS, JANET L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/315,298	Applicant(s) TENG ET AL.	
	Examiner Janet L Epps-Ford, Ph.D.	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,12,13,15,17-20,46,48-64,80 and 83-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10,12,13,15,17-20,46,48-64,80 and 83-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *26* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-28-2002 and 11-20-2001 has been entered.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-3, 5-7, 10, 17, 19-20, 46, 48, 54, 59-60, and 62-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Kawai et al. Claim 1 is drawn to a composition comprising at least one oligonucleotide in an emulsion and at least one penetration enhancer selected from surfactants, fatty acids, bile salts, chelating agents, non-chelating non-surfactant molecules, and combinations thereof. Claim 2 recites wherein said oligonucleotide is an antisense oligonucleotide. Claim 3 recites wherein said oligonucleotide modulates expression of a cellular adhesion protein, modulates a rate of cellular proliferation, or has biological activity against eukaryotic pathogens or retroviruses. Claim 5 recites wherein said emulsion is selected from the group consisting of an oil-in-water emulsion, a water-in-oil emulsion, an oil-in-water emulsion and a water-in-oil-in-water emulsion. Claim 6 recites wherein said emulsion is a microemulsion. Claim 10 recites wherein said fatty acid is selected from capric acid. Claim 17, the composition

of claim 1, wherein said surfactant is polyoxyethylene-20-cetyl ether. Claims 19-20 recite the composition of claim 1 further comprising a carrier compound, wherein said compound is dextran sulfate.

Kawai et al. disclose lipid microsphere in fat emulsion as a carrier to transducing gene DNA (i.e., microemulsion). These compositions comprise at least a transducing gene DNA, wherein said transducing gene DNA is synthetic oligonucleotide, such as the so-called phosphorothioate type, or it is a structural gene integrated into a vector (page 13, last paragraph of Japanese translation). Moreover, the compositions of the Kawai et al. invention comprise a transducing-gene DNA; fat emulsion base of at least one kind chosen from a vegetable oil, triglyceride of the medium chain triglyceride of 8-12 carbon atoms (such as capric, lauric and caprylic acid, see page 16, paragraph [0013]), fatty acids of 6-18 carbon atoms (penetration enhancer); the emulsifier of at least one kind chosen from a phospholipid and a nonionic surface active agent; a cholesterol derivative; and water (see summary of the invention, page 3 of the Japanese translation). It is assumed from the reference that the emulsions are oil-in water emulsions since they are described in the Japenese translation as being fat emulsions wherein the water serves as the solvent (page 18, paragraph [0016] of translation).

The "transducing-gene DNA" of Kawai et al. is chosen from cancer suppression gene DNA, gene DNA of an interleukin-1, interleukin-2, interleukin-4, interleukin-6, interleukin-7, GM-CSF, TNF-alpha, interferon-c, PDGF (cell adhesion protein), HVS-tk, diptheria-toxin A, and cytosine deaminases (see 3rd paragraph of page 5, Japanese translation).

In another embodiment of Kawai et al., an emulsifier is distributed above the fat emulsion, wherein the emulsifier is a phospholipid or a nonionic surface active agent, wherein said agent is polyoxyethylene-(20)-ether (page 17, paragraph [0015]).

Moreover, the fat emulsions of Kawai et al. can be made to contain further additive agents, such as an isotonizing agent emulsification support agent, a stabilizer (for example, wherein said stabilizer is dextran see page 20, paragraph [0020]), and a pH manufacture agent (page 18, paragraph [0017]).

Kawai et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 46, 52-53, 56-57 and 59-61 are rejected under 35 U.S.C. 102(e) as being anticipated by New et al. (see entire document)

New et al. disclose formulations in oral dosage form (col. 1, lines 5-9) comprising a biologically active material, wherein said biologically active materials may also be oligonucleotides such as antisense oligonucleotides and their analogues (col. 7, lines 5-12), and a adsorption or penetration enhancer such as a bile salt (col. 3, lines 37-48). The bile salts of New et al. comprise both ursodeoxycholic acid and chenodeoxycholic acid. Additionally, the compounds of New et al. may also further comprise chelator molecules such as EDTA or ethylene glycol (col. 6, lines 35-41), and comprise an enteric coating (tablet form) to prevent dissolution in the stomach (col. 7, lines 36-50).

New et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

7. Claims 1-2, 4-7, 15, 46, 52-53, 55-58, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Hnatowich et al. (see entire document).

Hnatowich et al. disclose formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion (col. 20, lines 59-67). Additionally, the compositions of Hnatowich et al. may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (col. 19, lines 34-37). The formulations of Hnatowich may comprise antisense oligonucleotides (col. 8, lines 29-32) or peptide nucleic acid (col. 3, lines 33-40). In an alternative emodiment, the formulations of

Hnatowich may also comprise a chelator moiety, which may be covalently linked to the nucleic acid (col. 2, lines 59-65), wherein said chelator moiety is selected from citric acid, and EDTA (col. 20, lines 38-40). The therapeutic compositions of Hnatowich et al. can be formulated in a carrier or coating, wherein the formulation may comprise propylene glycol (col. 19, lines 48-58).

Hnatowich et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

8. Claims 46, 48-54 and 83 are rejected under 35 U.S.C. 102(e) as being anticipated by Bennett et al. Claim 46 recites composition comprising an oligonucleotide in oral dosage form, wherein said oligonucleotide comprises at least one modified covalent linkage, and further wherein oligonucleotide has a sequence according to SEQ ID NO: 1.

Bennett et al. (US Patent 5,843,738) disclose antisense oligonucleotides targeted to mRNA corresponding to the cell adhesion molecule human ICAM-1, and specifically wherein said antisense oligonucleotide has a sequence according to SEQ ID NO: 1. Additionally, Bennett et al. disclose compositions comprising said antisense oligonucleotides for oral administration (col. 9, line 11-15), and further wherein said antisense oligonucleotide comprises modified base modifications (col. 9, lines 46-48), sugar modifications (col. 10, lines 5-19), and phosphorothioate modifications (col. 9, lines 53-67). The modifications to the base, sugar and internucleoside linkage are preferred over native forms because of properties such as, for example, enhanced cellular uptake and increased stability in the presence of nucleases (col. 9, lines 49-51). The compositions for oral administration include capsules and tablets (col. 9, lines 24-26).

Bennett et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

9. Claims 46, 48, 53-54, 59-60, 63 and 86 are rejected under 35 U.S.C. 102(e) as being anticipated by Nielsen et al. Claim 46 recites composition comprising an oligonucleotide in oral dosage form, wherein said oligonucleotide comprises at least one modified covalent linkage, and further wherein oligonucleotide has a sequence according to SEQ ID NO: 48.

Nielsen et al. discloses pharmaceutical compositions that are intended for application to or through the mucosa of an animal, wherein the mucosa is preferably selected from oral, nasal, vaginal, rectal, aural, lung, and gastrointestinal mucosa (page 3, lines 4-8) . In one embodiment of the Nielsen et al. invention, the pharmaceutical composition comprises a biologically active substance, wherein said substance is ISIS-2922 (page 14, lines 19-22), which is an anti-herpes virus agent that is a phosphorothioate modified antisense oligonucleotide according to SEQ ID NO: 48 of the instant application (see also the Registry report of the sequence of ISIS-2922).

The compositions of Nielsen et al. that are specifically for oral administration may comprise pharmaceutically acceptable carriers or excipients, which may include (*inter alia*) penetration enhancers, ointment bases, excipients, and chelating agents (page 22, lines 5-12). The ointment bases of Nielsen et al. include fatty acids such as vegetable oils, and palmitate (page 23, lines 9-11).

Nielsen et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 12-13, 60-61, 80, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawai et al. in view of New et al., Bennett et al. (5,843,738), and Nielsen et al.

The discussion of Kawai et al. set forth above is incorporated here. However, Kawai et al. does not disclose compositions comprising and emulsion and an oligonucleotide, and a bile salt, wherein said bile salt is selected from cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, or glycholic acid, or wherein said composition comprises a combination of at least one fatty acid and at least one bile salt. Additionally, Kawai et al. does not teach wherein the antisense oligonucleotide targeting a cellular adhesion protein comprises a sequence according to SEQ ID NO: 1, 55, 2, 16, 19, 48-54, or 56-58.

New et al. teach that compositions comprising bile salts improve absorption of biologically active materials because of they increase the permeability of cell membranes of epithelial cells. New et al. teach that in combination with the bile salt, a buffering agent (such as bicarbonate) to adjust the pH of the gut to a pH value of from 7.5 to 9, in order to increase the therapeutic index of the bile salts to the point where they could be used in pharmaceutical compostions (col. 2, lines 14-59).

Bennett et al. (US Patent 5,843,738) disclose antisense oligonucleotides targeted to mRNA corresponding to the cell adhesion molecule human ICAM-1. and specifically where said antisense oligonucleotide has a sequence according to SEQ ID NO : 1. Additionally, Bennett et al. disclose compositions comprising said antisense oligonucleotides for oral administration, and further wherein

Nielsen et al. disclose the antisense oligonucleotide according to SEQ ID NO: 48 (ISIS-2922), this antisense oligonucleotide is an anti-herpes virus agent.

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the compositions of Kawai et al. to further comprise bile salts, or to comprise the oligonucleotides disclosed in Bennett et al. and Nielsen et al. One of ordinary skill in the art would have been motivated to make this modification since the compositions of Kawai et al. are intended to provide carriers suitable for transducing gene DNA associated with cancer suppression genes, and DNA relevant to viral illness, and the antisense oligonucleotides of Bennett et al. and Nielsen et al. are disclosed as being useful for inhibiting the expression of genes associated with cancer (See Bennett et al., col. 6, lines 1-5) and viral infection (see abstract of Nielsen et al.), respectively. Moreover, one of ordinary skill in the art would have been motivated to modify the compositions of Kawai et al. with the bile salts of New et al. for the expressed benefits of the presence of bile salts in pharmaceutical compositions according to New et al., specifically wherein the bile salts function to improve absorption of biologically active materials into cells.

Therefore, the invention as a whole is *prima-facie* obvious over Kawai et al. in view of Bennett et al. and New et al.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 12 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites a composition of claim 1 wherein said bile salt is "polyoxyethylene-9-lauryl ether." This claim is vague and indefinite since one of ordinary skill in the art would recognize that an ether compound is not a salt.

Claim 50 recites the composition of claim 49 wherein "said modified sugar moiety has a substitution or addition at the 2'position of a moiety selected from the group consisting of –OH,...." The recitation of the group "-OH" in this claim is vague and indefinite since this group represents the native state of the 2'-position of the sugar moiety in an oligonucleotide. The –OH group does not represent a substitution or addition of the 2' position of a sugar moiety.

Claim 50 recites the narrow limitation: –O(CH2)nCH3 (where n= 1 to about 10), and the broader limitation: –O-alkyl group, in the same claim. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

The term "improving" in claim 50 is a relative term, which renders the claim indefinite. The term "improving" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. In the instant case, the metes and bounds of the phrases "improving the pharmacokinetic properties of an oligonucleotide," and "improving the pharmacodynamic properties of an oligonucleotide," are vague and indefinite since the scope of the term "improving" as used in this context is unclear.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
October 22, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635